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Discussion

Dr Scott M. Bradley *(Charleston, SC).* That was an excellent presentation on a topic that is clearly a challenge to everyone in the room. I thought that the information on the relative importance of low birth weight versus prematurity was particularly interesting, as was the growth velocity that can be expected in these low-birth-weight babies. I do have a couple of questions about the ways in which you have chosen to analyze your data.

The first question has to do with the 2 groups, which you call ''early'' and ''delayed.'' This differentiation was based on your retrospective assessment of the goal of the management team at the time that the patient presented. I commend you for going through all of those charts and figuring that out. Nonetheless, some of the patients in the delayed group underwent intervention within the first 1 to 2 weeks of life, which would not be considered very delayed and certainly not long enough to expect much growth. Do you have any information for us on the ages at intervention in the early group and whether there was overlap with what you call the delayed group?

Dr Hickey. Thank you very much, Dr Bradley, for your questions.

In terms of the categorization of patients, it is very difficult retrospectively and it would be great to do a prospective study, but that is simply impractical or impossible.

Rather than opt for procedure-based categories, for example, palliation or repair, we wanted to categorize in terms of completely deviating from the strategy. As best as I can, I think I have done that.

In terms of the ages of the 2 groups, patients in the early group were generally all intervened on the next available appropriate clinical slot in the neonatal period after presenting, so within the first 2 to 3 weeks after birth, whereas the mean age at intervention for the delayed group was on average about 8 weeks later. Of course, we had a number of deaths even within 1 to 2 weeks of being delayed.

Dr Bradley. It appears that if the early group was intervened on within the first 2 to 3 weeks after birth, there was significant overlap between the early and the delayed groups. That would probably be good information to put in the article.

Would it have been more clear-cut to simply analyze the patients on the basis of their age at intervention as either a continuous or a categorical variable, rather than trying to look back and determine the intentions of the team at the time, which was up to 10 years ago?

Dr Hickey. Certainly you can look at age at intervention, and we have done so in several other series. We know age at intervention is a very important variable. We specifically wanted to go back to the decision-making algorithm from the outset and make a decision-making analysis rather than just a risk-hazard-based analysis in retrospect.

Dr Bradley. I want to ask about a topic that you mentioned-the type of interventions in the 2 groups. Many of these patients were candidates for more than 1 intervention, for example, in tetralogy of Fallot, complete repair versus palliation with a shunt, in hypoplastic left heart syndrome, Norwood versus hybrid procedure. I assume that some of your patients underwent catheterization interventions, for example, balloon septostomy in patients with transposition and balloon aortic valvotomy in patients with aortic stenosis. Other catheterization interventions, while not routine, could be considered in selected patients, for example, stenting the outflow tract or the ductus in tetralogy or pulmonary atresia. Do you have any analysis of the breakdown of the types of intervention in your 2 groups: complete repair versus palliation versus catheterization laboratory?

Dr Hickey. It was our hope and intention from the outset that we might end up with some homogeneous patient groups, either in terms of diagnosis or in terms of interventional strategy, that we could then compare. It was very clear from the outset, though, that that was not going to be the case. This is actually quite an uncommon problem if you consider 80 patients over 10 years. We have a catchment area of about 13 million at Toronto. This is actually quite an unusual dilemma, although it is one we are all very familiar with. That is why we have such a heterogeneous bunch. Therefore, it is very difficult to compare one specific interventional strategy versus another. We have not been able to do that.

In terms of the range of options for each child, that exists for a normal-birth-weight child. Even for a child of normal birth weight with tetralogy or truncus or whatever, there can be different management strategies. We were only interested if we completely deviated and did something different because of the very low birth weight.

Dr Bradley. Fair enough. I think it would be useful to include some information on whether you are talking about complete repairs or palliation, especially in the early group. Although you did factor patient diagnosis into your risk-adjustment analyses, I would think you could enter complete repair versus palliation into that analysis as well.

One final question: You have given us some valuable information on the growth velocity that we can actually expect in these low-birth-weight patients if we do decide to take a wait-and-feed approach. Growth is generally more effective on enteral feeding than on total parenteral nutrition. However, many practitioners are reluctant to enterally feed a premature, low-birth-weight baby, especially if the infant is receiving a prostaglandin infusion. Can you tell us how the babies in your delayed group were approached in terms of feeding to achieve growth, from your review of charts, or what your approach would be now, particularly in a baby who is receiving a prostaglandin infusion?

Dr Hickey. Unfortunately, I cannot elaborate much on that information because we did not have those data. Nor am I, by any

stretch of the imagination, an expert on nutrition in these small infants. Nevertheless, in our intensive care unit we aggressively try to enterally feed all our infants unless there is a strong reason to do otherwise. Obviously, we use fortified feeds with dietician advice and all that sort of thing.

In terms of the difference between the growth rates, I was most struck by the difference, especially the infants with coarctation, which seemed to grow at a very high level of statistical significance at a very low rate. That to us suggests that of all the groups, patients with coarctation are maybe the ones on whom we should operate early. Indeed, that is what we do now routinely, down to 1.4 to 1.5 kg.

I have just one final comment about your previous comments about palliation: At Sick Kids we have a very high threshold for palliative strategies. In the mid-1990s we switched, for example, from using any shunts for patients with tetralogy; it is rare, in fact, that we use bands or shunts in children now. Indeed, in this series they were very infrequent occurrences.

The data on long-term prostaglandin therapy, especially, is encouraging us to now explore other catheter-based approaches that can be used instead of long-term prostaglandin, especially subxiphoid approaches for tiny infants.

Dr Bradley. Fair enough. I think it is a very nice study. It is a relatively large group of patients with these issues. If you could provide some of this additional information in the article, it would be of interest to the readers.

Dr V. Mohan Reddy *(Stanford, Calif).* Dr Hickey, I would like to ask you a few questions. I know you looked at a lot of risk factors, but did you look at patients who were dependent for a prolonged period for mechanical ventilation or prostaglandins versus patients who are not dependent?

Dr Hickey. As subgroups, no, but they were both included as risk factors. We had acquired respiratory morbidity as a risk factor from the outset as baseline.

Dr Reddy. From the data, I could see that patients whose treatment was delayed had a significantly higher incidence of complications and there was also some mortality.

Dr Hickey. That is true.

Dr Reddy. But overall, there was no difference. What do you think accounted for the mortality in the early group to equalize it?

Dr Hickey. Intuitively, the assumption is that intervening in very small children is of elevated risk. We assume that the greater morbidity and mortality burden is in some way outweighed by the risk of intervening on these very small children.

Equally, we fully acknowledge that there are important differences within the patient groups, which is why we have tried to look at it in multiple different ways; but we still are not seeing an important difference between the 2 strategies.

Dr Reddy. Most likely, it could be technical. As with all technical operations, we gradually get better when we do the operation over time. I can assure you that even though the patient's weight increases from 1.5 kg to 2 kg or 2.2 kg, the heart is not going to be much bigger than 10 mg or 20 mg. Thus, I do not think it technically makes a huge difference. I think it is more in the mind than in actually doing the operation.

Dr Hickey. In terms of the risk of actually performing the operation, I agree, the technical aspects are very valid. Furthermore, certainly most here will know that your group at Stanford has managed to mitigate some of these issues, perhaps because of your experience with operating on fetal animals. You are much more attuned to operate on the infant weighing 1.1 to 1.2 kg. Those are technical hurdles that others would have to overcome if they adopt that aggressive early approach.

However, certainly these smaller children are also physiologically different. There are immunologic risk factors, there are nutrition factors, they are much more prone to other complications, cerebral bleeds, that sort of thing, and so there are differences.

There is just one thing about this weight that I find fascinating. I have done subanalyses looking at the normal-birth-weight range, and even within the normal-birth-weight range, birth weight is a very strong determinant of risk, which is a very curious and interesting fact.

Dr Reddy. I think this is very important information to have available. However, I personally think that the patient should be individualized, not necessarily bunched into 1 of 2 categories, early and late or left-sided versus right-sided lesions. If the patients are dependent on a ventilator or requiring prolonged prostaglandins in the infusions, then we would generally tend to intervene. However, if the patient can be extubated and can be fed normally or can be taken off prostaglandin, I think the operation can certainly be delayed.

Dr Hickey. We would agree with you. We do not think our data can strongly advocate for one approach or the other, so we agree that the approach needs to be individualized. We also will intervene very early on very small patients with truncus or coarctation if we think that that child clinically is of acceptable risk to undergo an operation early. However, we are also reassured that if we choose to take a delayed approach, we are not taking on an excessive morbidity risk.

Dr Reddy. I also think more recent data suggest that the gestational age may have an impact on the neurologic injury and the brain maturation. That might be a more common factor for us to delay surgery in these patients, if we can safely.

Dr Hickey. Certainly. Dr Gaynor's group has done a lot of work showing very nicely that babies born at term with certain lesions are developmentally very immature, and that is a strong determinant of neurologic injury. Therefore, although we have focused on survival as the end point, we have not taken into account the morbidity burden in the long-term with either strategy, and that may be just as important.

Dr Reddy. One last question. Do you have any plans to do a prospective study in this regard?

Dr Hickey. I think the numbers that we have generated, 80 over 10 years from 1600 patients, really preclude that.

Dr Frank A. Pigula *(Boston, Mass).* My question is whether it is really fair to equate weight gain with growth in children who are receiving prostaglandins and are intubated with various means of nutritional support. I am not sure that they are really the same thing in those patients.

My other comment is that in analysis of our unit with these patients, their gestational age has been more important than their size. We can operate on very small patients, but we cannot make them older when we operate on them. Could you please address the age versus size issue?

Dr Hickey. When we pitched prematurity, that is, gestational age to birth weight, consistently birth weight was the more reliable determinant. That is because prematurity, although very important,

as our data showed, is important because of the whole host of problems that come with it—certain lesions, certain other comorbidities, certain genetic syndromes, and such like. That's what the data were telling us was accounting for the risk of prematurity. Birth weight per se is a more reliable determinant as an independent risk factor for death.

Dr Pigula. That is interesting. That is a little bit counter to what we have seen in our group.

Dr Christian Pizarro *(Wilmington, Del).* That was a beautiful job. I am unclear about how patients were fed and how the choice was made. I saw you encountered a lot of gastrointestinal complications. A common problem we all face is that we see a tiny little baby and want to use enteral feeds, but we are hesitant, particularly in someone who has a shunt at the arterial level, such as an infant with truncus or hypoplastic left heart syndrome. What was the choice regarding feeding or nutrition in those patients, and could that be in any way related to the speed of weight gain?

Dr Hickey. That is entirely possible. I do not have all the data on the mechanisms of which patients were fed. Certainly gastrointestinal complications were common, as you expect in these very small children. We try to feed them enterally if at all possible to avoid necrotizing enterocolitis and other complications, but I do not have the specifics of that information.

In terms of weight gain, I am not sure what actually gave rise to the differences that we saw in weight gain. However, the category that really stuck out was patients with coarctation. They are not normally the infants who have all the other comorbidities, and yet their weight gain was very poor to a high level of significance.